**2. Prevention of severe nausea and vomiting**: The older antipsy- chotics (most commonly, prochlorperazine [PROE-clor-PEAR-a-zeen]) are useful in the treatment of drug-induced nausea (see p. 358). However, nausea arising from motion should be treated with seda- tives, antihistamines, and anticholinergics, rather than with the pow- erful antipsychotic drugs. [Note: Transdermal scopolamine is a drug of choice for treatment of motion sickness.]

**3. Other uses**: The antipsychotic drugs can be used as tranquilizers to manage agitated and disruptive behavior, secondary to other disor- ders. Antipsychotics are used in combination with narcotic analge- sics for treatment of chronic pain with severe anxiety. Chlorpromazine is used to treat intractable hiccups. Although promethazine [proe- METH-a-zeen] is not an eff ective antipsychotic drug, this agent is used in treating pruritus because of its antihistaminic properties. Pimozide [PI-moe-zide] is primarily indicated for treatment of the motor and phonic tics of Tourette disorder. However, risperidone and haloperidol are also commonly prescribed for this tic disorder. Also, risperidone and aripiprazole are now approved for the management of the disruptive behavior and irritability secondary to autism.

**D. Absorption and metabolism**

 After oral administration, the antipsychotics show variable absorption that is unaff ected by food (except for ziprasidone [zi PRAY si done] and paliperidone [pal-ih-PEAR-ih-dohn], the absorption of which is increased with food). These agents readily pass into the brain, have a large vol- ume of distribution, bind well to plasma proteins, and are metabolized to many diff erent substances, usually by the cytochrome P450 system in the liver, particularly the CYP2D6, CYP1A2, and CYP3A4 isoenzymes. Some metabolites are active. Fluphenazine decanoate, haloperidol decanoate, risperidone microspheres, paliperidone palmitate, and olan- zapine pamoate are long-acting injectable (LAI) formulations of antip- sychotics that are administered via deep gluteal intramuscular injection or deltoid injection. These formulations have a therapeutic duration of action of up to 2 to 4 weeks and, therefore, are often used to treat out- patients and individuals who are noncompliant with oral medications. However, patients may still develop EPS, but the risk of EPS is lower with these LAI formulations compared to their respective oral formulations. The antipsychotic drugs produce some tolerance but little physical dependence.

**E. Adverse eff ects**

 Adverse eff ects of the antipsychotic drugs can occur in practically all patients and are signifi cant in about 80 percent (Figure 13.6). Although antipsychotic drugs have an array of adverse eff ects, their therapeutic index is high.

**1. Extrapyramidal side eff ects**: The inhibitory eff ects of dopamin- ergic neurons are normally balanced by the excitatory actions of cholinergic neurons in the striatum. Blocking dopamine receptors alters this balance, causing a relative excess of cholinergic infl uence, which results in extrapyramidal motor eff ects. The maximal risk of appearance of the movement disorders is time and dose depen- dent, with dystonias occurring within a few hours to days of treat- ment, followed by akathisias (the inability to remain seated due to motor restlessness) occurring within days to weeks. Parkinson-like symptoms of bradykinesia, rigidity, and tremor usually occur within weeks to months of initiating treatment. Tardive dyskinesia, which can be irreversible, may occur after months or years of treatment.

**a. Eff ect of anticholinergic drugs** : If cholinergic activity is also blocked, a new, more nearly normal balance is restored, and extrapyramidal eff ects are minimized. This can be achieved by administration of an anticholinergic drug, such as benztropine. The therapeutic trade-off will be fewer EPS in exchange for the side effect of muscarinic-receptor blockade. [Note: Sometimes, the parkinsonian symptoms and akathisias persist despite the use of anticholinergic drugs.] Those drugs that exhibit strong anticholinergic activity, such as thioridazine, show fewer extrapyramidal disturbances, because the cholinergic activity is strongly dampened. This contrasts with haloperidol and fluphenazine, which have low anticholinergic activity and produce extrapyramidal effects more frequently because of the preferential blocking of dopaminergic transmission without the blocking of cholinergic activity. Akathisia may respond better to β blockers or benzodiazepines rather than anticholinergic medications.

**2. Tardive dyskinesia**: Long-term treatment with antipsychotics can cause this motor disorder. Patients display involuntary movements, including bilateral and facial jaw movements and “fly-catching” motions of the tongue. A prolonged holiday from antipsychot- ics may cause the symptoms to diminish or disappear within a few months. However, in many individuals, tardive dyskinesia is irrevers- ible and persists after discontinuation of therapy. Tardive dyskinesia is postulated to result from an increased number of dopamine recep- tors that are synthesized as a compensatory response to long-term dopamine-receptor blockade. This makes the neuron supersensitive to the actions of dopamine, and it allows the dopaminergic input to this structure to overpower the cholinergic input, causing excess movement in the patient. Traditional anti-EPS medications do not generally improve tardive dyskinesia and may actually worsen this condition.

3. **Antipsychotic malignant syndrome**: This potentially fatal reac- tion to antipsychotic drugs is characterized by muscle rigidity, fever, altered mental status and stupor, unstable blood pressure, and myo- globinemia. Treatment necessitates discontinuation of the antipsy- chotic agent and supportive therapy. Administration of dantrolene or bromocriptine may be helpful.

**4. Other effects**: Drowsiness occurs due to CNS depression and anti- histaminic effects, usually during the first few weeks of treatment. Confusion sometimes results. Those antipsychotic agents with potent antimuscarinic activity often produce dry mouth, urinary retention, constipation, and loss of accommodation. Others may block α-adrenergic receptors, resulting in lowered blood pressure and orthostatic hypotension. The antipsychotics depress the hypo- thalamus, affecting thermoregulation and causing amenorrhea, galactorrhea, gynecomastia, infertility, and impotence. Significant weight gain is often a reason for noncompliance. It is also recom- mended that glucose and lipid profiles be monitored in patients tak- ing antipsychotics due to the potential for the second-generation agents to increase these laboratory parameters and the possible exacerbation of preexisting diabetes mellitus or hyperlipidemia.

**5. Cautions and contraindications**: Acute agitation accompanying withdrawal from alcohol or other drugs may be aggravated by the antipsychotics. Stabilization with a simple sedative, such as a benzo- diazepine, is the preferred treatment. All antipsychotics may lower the seizure threshold and should be used cautiously in patients with sei- zure disorders. Therefore, the antipsychotics can also aggravate pre- existing epilepsy and should be used with caution in patients with epilepsy. The high incidence of agranulocytosis with clozapine may limit its use to patients who are resistant to other drugs. All of the sec- ond-generation antipsychotics also carry the warning of increased risk for mortality when used in elderly patients with dementia- related behavioral disturbances and psychosis. Antipsychotics used in patients with mood disorders should also be monitored for wors- ening of mood and suicidal ideation or behaviors.

**F. Maintenance treatment**

 Patients who have had two or more psychotic episodes, secondary to schizophrenia, should receive maintenance therapy for at least 5 years, and some experts prefer indefi nite therapy. There has been a greater emphasis in research and practice on identifying and aggressively man- aging fi rst-episode psychosis to determine the benefi ts of antipsychotic agents in this population. Low doses of antipsychotic drugs are not as eff ective as higher-dose maintenance therapy in preventing relapse. The rate of relapse may be lower with second generation drugs (Figure 13.7). Figure 13.8 summarizes the therapeutic uses of some of the antip- sychotic drugs.